Encephalitis after administration of live measles vaccine

FRANKLIN JAGDIS,* MD, BS; CLAIRE LANGSTON,† MD; MARC GURWITH,‡ MD, FRCP[C], FACP

Summary: In a previously well child with no evidence of pre-existing immunologic defect a fatal encephalitis developed 10 days after administration of measles vaccine. There was pathologic evidence of an early viral encephalitis characterized by perivascular mononuclear infiltrates. Although the virus was not recovered, the diagnosis of a measles virus infection and encephalitis is supported by the postmortem findings of Warthin-Finkeldey cells in lymphoid tissues, an intranuclear inclusion in the brain and histologic changes of encephalitis.

Résumé: *Cas d'encéphalite après administration d'un vaccin antimorbilleux vivant*

Chez un enfant auparavant bien portant et qui ne présentait aucun signe d'un défaut immunologique préexistant, survint une encéphalite fatale, 10 jours après administration d'un vaccin contre la rougeole. On nota des signes pathologiques d'une encéphalite virale précoce, caractérisée par des infiltrats mononucléaires périvasculaires. Bien que le virus n'ait pu être récupéré, le diagnostic d'une infection par le virus de la rougeole et de l'encéphalite a pu être confirmé par les découvertes nécropsiques: présence des cellules de Warthin-Finkeldey dans le tissu lymphoïde, inclusion intranucléaire dans le cerveau et modifications histologiques de l'encéphalite.

Immunization with live attenuated measles virus has greatly lowered the incidence of natural measles in North America over the last 10 years.[1] The vaccine virus confers immunity with few adverse effects. This report describes a patient with encephalitis that developed after the administration of live measles virus vaccine.

Case report

A 13-month-old white girl was admitted to the Children's Centre, Health Sciences Centre, Winnipeg on July 24, 1973. She had been febrile and vomiting for 2 days before admission. On the day of admission her pediatrician described involuntary jerking movements of her limbs, interpreted as febrile convulsions. There were no symptoms of an upper respiratory tract illness. Ten days before admission she had received 0.5 ml of further attenuated Enders live measles virus vaccine prepared in chick embryo cell lines.

The past history was unremarkable except for three ear infections during the previous 9 months and a bronchial infection necessitating antibiotic therapy 4 weeks before admission. She was immunized with diphtheria-pertussis-tetanus vaccine and oral poliomyelitis vaccine at 3, 4 and 5 months of age with no untoward effects.

She was irritable but afebrile. Her growth measurements were normal. There were no skin rashes or Koplik's spots. She was fully conscious and results of central nervous system examination, including funduscopy, were normal.

The chest radiograph was normal. The hemoglobin value was 12.3 g/dl and the leukocyte count 9800/mm^3 (differential: mature neutrophils, 51%; young neutrophils, 21%; lymphocytes, 21%; monocytes, 6%; and basophils, 1%). Values of serum electrolytes, bilirubin, lactic dehydrogenase, glutamic transaminase, alkaline phosphatase, total proteins and blood glucose and urea nitrogen were normal. The serum was negative for barbiturates and the salicylate value was 6 mg/dl.

The cerebrospinal fluid, which was turbid, contained 74 lymphocytes and 5 neutrophils per mm^3; the protein value was 494 mg/dl and the glucose value 80 mg/dl. Gram's staining demonstrated no organisms, and culture for bacteria was negative.

After the lumbar puncture intravenous administration of ampicillin, 400 mg/kg·d, was started. About 4 hours after admission she had a generalized convulsion. This was treated with diazepam, 2 mg and phenobarbital, 35 mg intravenously. Apnea then occurred. She was intubated and mechanical ventilation was begun. Both pupils were dilated and nonreactive to light. Funduscopy revealed bilateral papilledema. Dexamethasone therapy was begun. An echo encephalogram did not reveal any midline shift. Electroencephalograms at 12, 36 and 60 hours after admission showed electrocerebral silence. Ventilatory assistance was discontinued and the patient died.

Autopsy findings

The gross autopsy examination was completed within 3 hours of death. The brain was removed immediately. It was soft and swollen, with gyral flattening and cerebellar tonsillar herniation. All organs save the brain were well preserved. The thymus was small. Portions of the brain and lungs were fixed in glutaraldehyde for electron microscopy.

Microscopic examination of the brain showed cerebral edema and vascular congestion. Perivascular lymphocyte infiltration was most evident in the brain stem

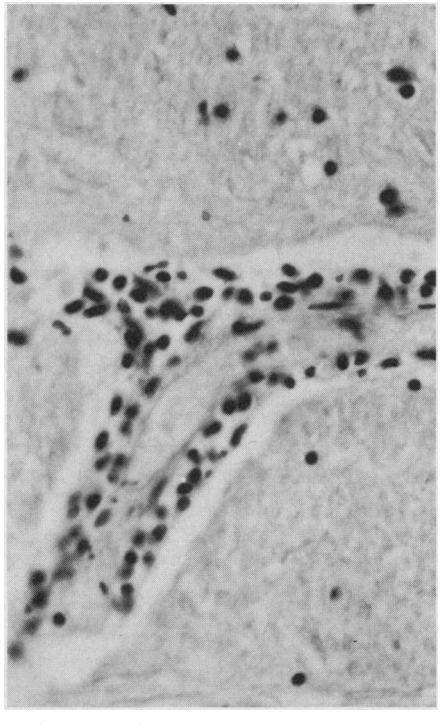

FIG. 1—Perivascular lymphocyte infiltrate in widespread areas of the brain (hematoxylin-eosin; x380).

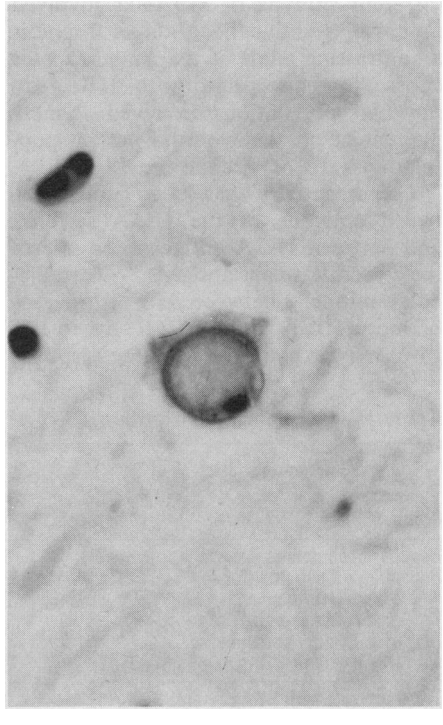

FIG. 2—Neuron in ventral pons containing single eosinophilic intranuclear inclusion (hematoxylin-eosin; x1140).

From the departments of pediatrics,*† pathology,† medicine and medical microbiology,‡ University of Manitoba, and the Health Sciences Centre, Winnipeg

*Now a fellow of the Medical Research Council of Canada at the section of infectious and immunologic diseases, University of California, Davis, CA

Reprint requests to: Dr. M. Gurwith, Division of infectious diseases, Health Sciences Centre, 700 William Ave., Winnipeg, Man. R3E 0Z3

(Fig. 1). A single large eosinophilic (Cowdry type A) intranuclear inclusion was noted in this area as well (Fig. 2). Fibrin was present in many of the capillaries within the central nervous system. Small numbers of eosinophilic neurons were noted in scattered areas. Fragments of degenerating cerebellar cortex surrounded the spinal cord.

Warthin-Finkeldey giant cells were present in sections of lymphoid tissue from the base of the tongue and epiglottis (Fig. 3); they were not identified in any other site. All lymphoid tissues were well developed. There was no morphologic evidence of an immune deficiency. There was a mild generalized lymphoid hyperplasia. The thymus showed acute involution of an apparently previously normal gland. No abnormal features were noted in any other organ system.

Electron microscopy of the brain revealed poor preservation of tissue with definite autolytic changes. No virus particles were identified. The lung tissue was normal on electron microscopy.

Virologic studies

Cultures: The following specimens were collected: (a) antemortem: tracheal secretions, urine, blood; (b) postmortem: tracheal swab, blood, brain and liver tissue. The tissue specimens were transported in Hank's balanced salt solution and inoculated into human amnion, rhesus monkey kidney, African green monkey kidney and WI 38 cell cultures. All cultures were maintained for 30 days, during which two blind passages and the hemadsorption test for myxoviruses were done using guinea pig erythrocytes. Brain tissue and blood were also inoculated intraperitoneally and intracerebrally into suckling Swiss-Webster mice, which were observed for 30 days. There was no evidence of the presence of a virus in the tissue cultures or the mice.

Serologic studies: These were limited because the patient died 3 days after admission. There were no increases in titre in samples from day 1 and day 3 on testing to herpes simplex, mumps, measles, lymphocytic choriomeningitis, ECHO 9, St. Louis encephalitis, California encephalitis or western equine encephalomyelitis viruses (Table I).

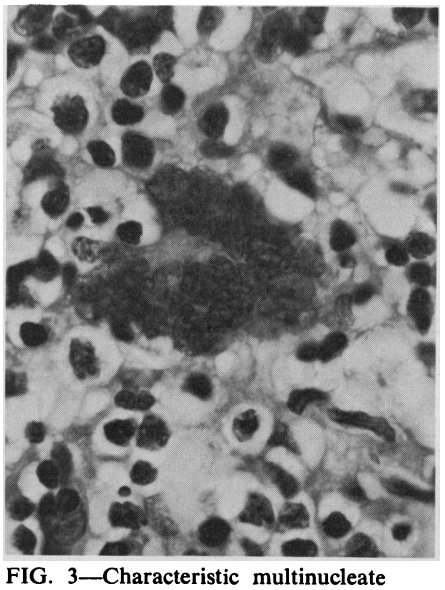

FIG. 3—Characteristic multinucleate (Warthin-Finkeldey) giant cell in pharyngeal lymphoid tissue (hematoxylin-eosin; x1520, reduced by 50%).

Discussion

Natural measles infection is associated with a high degree of morbidity. Neurotropism is a prominent property of wild measles virus and overt encephalitis is estimated to occur in approximately 0.1% of infected children.[1] The use of live attenuated viruses produces immunity with minimal adverse effects.[1,2]

A report of 84 cases of neurologic disorders developing after measles vaccine administration was published in 1973.[3] Of the 84 cases 13 were caused by agents other than measles virus, 1 was a case of subacute sclerosing panencephalitis and 11 were cases of febrile convulsions. The remaining 59 cases were of severe acute neurologic disease; 45 cases occurred 6 to 15 days after vaccination, the period of maximal viral replication and viremia. The mortality rate was 10%. The overall rate of neurologic complications was 1.16 per million vaccine doses.

In 1973 six more cases of neurologic disorders developing after live measles vaccination were reported.[1] Although clinical data were incomplete, three of these cases appeared to have no other possible cause and occurred between days 6 and 15 after vaccination. Another trend noted was the declining incidence of neurologic disorders. In 1963 and 1966 the rate was 1.25 and 1.12 per million vaccine doses, respectively, whereas in 1971 and 1972 it was 0.12 and 0.73.[1,3]

Detailed clinical descriptions of neurologic disease developing after measles vaccination are scanty, but presentations include encephalitis, encephalomyelitis, aseptic meningitis and isolated cranial nerve palsies.[1,3-6] There is only one report of isolation of measles vaccine virus from the central nervous system: in a patient who presented 7 days post immunization with choreoathetosis and ataxia, virus was isolated from the cerebrospinal fluid.[6]

The onset of illness in our patient was during the expected period of viremia after measles immunization. No bacterial pathogen was identified, nor were the clinical findings compatible with a bacterial illness. There was no history of exposure to any illness, although a measles epidemic in the community was just ending.[7] The absence of rash and Koplik's spots suggests that the illness was not typical natural measles. Severe measles may be seen more frequently in immunologically compromised hosts, but encephalitis is not a usual feature. However, an accelerated form of subacute sclerosing panencephalitis has been described in these patients.[8] The presence of poliovirus antibodies (from the previous routine immunizations), the normal lymph node architecture and cellularity, and the well developed thymus with well defined Hassell's corpuscles make a primary immunologic deficiency syndrome unlikely. The clinical course and pathologic findings suggest that the child had a mild viral encephalitis with seizures. The subsequent apnea, cerebellar tonsillar herniation and death may have been more directly related to the seizures or their subsequent therapy, or both, than to the encephalitis.

No viruses were isolated from tracheal secretions, urine, blood or brain and liver tissue, although without cocultivation these viral studies cannot be considered optimal. Isolation of measles virus from the brain in wild measles encephalitis has been difficult to achieve without cocultivation, and the isolation of the vaccine virus from the brain in cases of acute encephalitis has not been reported.[9] The finding of perivascular mononuclear infiltrates in the brain is consistent with viral ence-

Table I—Specific viral antibody titres

Virus	Antibody titre	
	Day 1	Day 3
Rubeola		
(complement fixation test)	< 1:4	< 1:4
(hemagglutination inhibition test)	< 1:10	< 1:10
Mumps		
(viral antigen)	< 1:4	< 1:4
(soluble antigen)	< 1:4	< 1:4
Herpes simplex	1:4	1:4
Western equine encephalomyelitis	1:4	< 1:4
St. Louis encephalitis	< 1:4	< 1:4
California encephalitis	< 1:4	< 1:4
Lymphocytic choriomeningitis	1:4	1:4
ECHO 9	< 1:10	< 1:10
Poliovirus		
Type 1	1:40	1:8
Type 2	1:160	1:160
Type 3	1:80	1:160

phalitis. The additional finding of a Cowdry type A intranuclear inclusion in the brain stem suggests, but is not diagnostic of, a measles virus infection of the central nervous system.[10] It is difficult to explain why there was no measles antibody response, for antibody is detected in most children 10 to 12 days after infection with vaccine virus.[11] There was no evidence of deficiency in humoral or cellular immunity.

Encephalitis due to wild measles virus has been divided into five clinicopathologic types that seem to correspond to duration of illness.[12] That in our patient was similar to the acute inflammatory type, characterized by the presence of mononuclear cuffs surrounding vessels in both the Virchow-Robin spaces and in the tissues of the central nervous system. There is no demyelination in this relatively early form of measles encephalitis. The pathologic changes of encephalopathy due to measles vaccine virus have not been reported, to our knowledge. The findings in our patient are compatible with an early mild encephalitis due to direct involvement of the brain by the measles vaccine virus.

In wild measles infection Warthin-Finkeldey giant cells may be seen in the lymphoid tissues throughout the body. They consist of large numbers of nuclei in a cluster with scant cytoplasm.[13] The presence of these characteristic giant cells in the lymphoid tissues of the pharynx indicate that our patient had an infection with a measles virus at the time of death. Such cells have been described in small numbers in the lymphoid tissues of monkeys inoculated with measles vaccine strains[14] and in regional nodes draining the vaccination site in children receiving measles vaccine.[15,16] The paucity of these giant cells in our case is consistent with infection by measles vaccine virus.[14]

Clinically, the measles vaccine viruses appear to have negligible neurotropism,[17,18] although electroencephalographic changes have been described.[19] Vaccine viruses of the Schwartz and Beckenham 31 strains have grown and replicated on tissue culture of non-neuronal cells of human fetal brain.[20] A wide variety of vaccine strains, when inoculated intracerebrally into suckling animals, demonstrate neurotropism and are lethal.[21-24] In animals affected, multinucleate giant cells have been described in brain tissue.[22,24] Results of these tissue cultures and animal studies suggest that the presently available vaccines do possess some neurotropism.

Neurologic disorders developing after infection with wild measles virus far outnumber those occurring after immunization. Infrequent vaccine-related (or -induced) neurologic complications, such as reported here, should not be considered enough reason to alter current recommendations concerning measles vaccine administration.

We are indebted to Dr. I.L. Goldberg for referral of his patients, Dr. A.R. Ronald for criticisms, Mrs. R. Peeling and Mr. W. Stackiw for virologic studies and Dr. J. Hoogstraten for performing the electron microscopy.

References

1. *Measles Surveillance,* report no 9, 1972 summary, DHEW publ no (CDC) 74-8253. US Dept of Health, Education and Welfare, Public Health Service, Centre for Disease Control, Atlanta, Georgia, p 12, 8-9, 1973
2. KATZ SL, KEMPE CH, BLACK FL, et al: Studies on an attenuated measles-virus vaccine: VIII. General summary and evaluation of the results of vaccination. *N Engl J Med* 263: 180, 1960
3. LANDRIGAN PJ, WITTE JJ: Neurologic disorders following live measles virus vaccination. *JAMA* 223: 1459, 1973
4. PESTRI T: Encephalitis after live measles virus vaccine (C). *Can Med Assoc J* 94: 1133, 1966
5. SNYDER RD: Facial palsy following measles vaccination, a possible connection. *Pediatrics* 42: 215, 1968
6. FORMAN ML, CHERRY JD: Isolation of measles virus from the cerebrospinal fluid of a child with encephalitis following measles vaccination, in *Proceedings of the 77th Meeting of the American Pediatric Society,* Apr. 26-29, 1967, New Haven, CN, Am Pediatr Soc Inc, 1967, p 32
7. Health and Welfare Canada: Measles. *Epidemiol Bull* 17: 105, 1973
8. BREITFELD V, HASHIDA MD, SHERMAN FE, et al: Fatal measles infection in children with leukemia. *Lab Invest* 28: 279, 1973
9. TER MEULEN V, MÜLLER D, KACKELL Y, et al: Isolation of infectious measles virus in measles encephalitis. *Lancet* 2: 1172, 1972
10. ADAMS JM, BAIRD C, FILLOY L: Inclusion bodies in measles encephalitis. *JAMA* 195: 290, 1966
11. KRUGMAN S, GILES GP: Measles — the problem, in *International conference on the application of vaccines against viral, rickettsial and bacterial diseases of man,* Pan Am Health Org, Washington, 1971, pp 195-202
12. BÉRARD-BADIER M, GASTAUT A, PAYAN H: Comparative clinico-pathological study of one early and two late cases of measles encephalitis, in *Encephalitides,* edited by VAN BOGAERT L, Amsterdam, Elsevier Pub 1961, pp 106-123
13. WARTHIN AS: Occurrence of numerous large giant cells in the tonsils and pharyngeal mucosa in the prodromal stage of measles. *Arch Pathol* 11: 864, 1931
14. YAMANOUCHI K, EGASHIRA Y, UCHIDA N, et al: Giant cell formation in lymphoid tissues of monkeys inoculated with various strains of measles virus. *Jap J Med Sci Biol* 23: 131, 1970
15. ALLEN MS JR, TALBOT WH, MCDONALD RM: Atypical lymph-node hyperplasia after administration of attenuated, live measles vaccine. *N Engl J Med* 274: 677, 1966
16. DORFMAN RF, HERWEG JC: Live attenuated measles vaccine. Inguinal adenopathy complicating administration. *JAMA* 198: 320, 1966
17. ST GEME JW, WRIGHT FS, JONES F, et al: Failure to detect subtle neurotropism of live, attenuated measles virus vaccine. *J Pediatr* 70: 36, 1967
18. GIBBS FA, ROSENTHAL IM: Electroencephalography in natural and attenuated measles. *Am J Dis Child* 103: 395, 1962
19. PAMPLIGIONE G, GRIFFITH AH, BRAMWELL EC: Transient cerebral changes after vaccination against measles. *Lancet* 2: 5, 1971
20. WEBB HE, ILLAVIA SJ, LAURENCE GD: Measles-vaccine viruses in tissue-culture of non-neuronal cells of human fetal brain. *Lancet* 2: 4, 1971
21. ZDNEK J, NORRBY E, MARUSYK H: Neurotropism of measles virus variants in hamsters. *J Infect Dis* 124: 553, 1971
22. ALBRECHT P, SCHUMACHER HP: Neurotropic properties of measles virus in hamsters and mice. *J Infect Dis* 124: 86, 1971
23. MIRCHAMSY H, RAZAVI J, AHURAI P: Pathogenesis of vaccine strains of measles virus in suckling hamsters. *Acta Virol (Praha)* 16: 77, 1972
24. SHISIDO A, KATOW S, KOBUNE K, et al: Growth of measles virus in nervous tissues. *Jap J Med Sci Biol* 26: 103, 1973